Severe Insulin-Resistant Diabetes Mellitus Associated with Hypereosinophilic Syndrome

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We describe a 52-year-old male manifesting severe insulin resistance associated with hypereosinophilic syndrome (HES). Diabetes mellitus was initially well-controlled by an oral hypoglycemic agent, and thereafter by human insulin. Due to the progression of hypereosinophilia, hepatosplenomegaly and peripheral lymphoadenopathy, severe insulin resistance associated with diabetic ketoacidosis occurred repeatedly, despite intravenous administration of over 1,000 U per day of human insulin. A high plasma insulin-binding capacity as determined by Scatchard analysis was consistent with insulin antibody-mediated resistance. The diagnosis of HES was made due to the persistent elevation of eosinophil count and associated liver and cardiac damage. Glucocorticoid therapy successfully achieved both reducing clinical symptoms and improving glycemic control.

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Introduction

Insulin antibodies can be demonstrated in nearly all patients after starting therapy with animal insulin and they may be directed against human insulin (1). High levels of circulating anti-insulin antibodies may contribute to insulin resistance. However, in most patients, the presence of anti-insulin antibodies does not necessarily affect glycemic control, and antibody-mediated insulin resistance is rare and nearly all cases have been demonstrated in diabetic patients receiving animal insulin (2-4). There have been only a few reported cases of insulin resistance in which human insulin was the antigen (5).

We recently treated a patient with severe insulin resistance due to anti-insulin antibody during human insulin treatment. He had persistent marked eosinophilia with hepatosplenomegaly and lymphoadenopathy, and died due to cardiac involvement. We discuss here the significant interaction between immunological disorders in hypereosinophilic syndrome (HES) and the cause of antibody-mediated insulin resistance.

Case Report

A 52-year-old male was admitted to our hospital in April 1992, because of poor glycemic control in spite of large doses of human insulin. He had a history of lung tuberculosis but had not traveled recently or taken care of any animals. He was first diagnosed with diabetes mellitus in 1975 and was treated typically with an oral hypoglycemic agent, but was transiently treated with animal insulin for only 10 days. In 1989, human insulin therapy was administered due to weight loss and hyperglycemia, and he was well-controlled by 40 U of human NPH insulin although he sometimes experienced pruritus with redness at injection sites. Hypereosinophilia and hepatosplenomegaly were already noted before continuous insulin therapy. In 1992, the patient’s symptoms began four months prior to admission and progressed to include weight loss, diarrhea, inguinal lymphnode swelling, and severe resistance to insulin therapy. Although the human insulin dose was increased, he was often prone to diabetic ketoacidosis.

On admission, physical examination revealed the patient to be slightly drowsy. The liver and spleen were palpable 5 cm below the right costal border and 7 cm at the longest part, respectively. There were several enlarged cervical and inguinal lymphnodes with no tenderness and good mobility. Muscle atrophy was prominent in the interosseous muscle of the back of the hands and the crural muscle. Muscle weakness was observed on the left side. Sensation was disturbed in the peripheral extremities of the glove and stocking type.

Urinalysis showed strong positive glucose and ketone levels and no protein. Blood gas analysis revealed severe metabolic...
acidosis (pH 7.168, PCO₂ 27.2 mmHg, PO₂ 97.0 mmHg, HCO₃⁻ 10.0 mM/l, and BE - 16.4 mM/l). Fasting plasma glucose and HbA₁c levels were 622 mg/dl and 11.1%, respectively. White blood cell count was 15,100/mm³ with 70% eosinophils noted. Blood chemistries including liver and kidney functions and electrolytes were nearly normal. ECG revealed normal sinus rhythm and no abnormality. UCG revealed slight left ventricular hypertrophy and no parietal thrombus.

After admission, the patient became more refractory to subcutaneous insulin therapy and was switched to intravenous human insulin (Fig. 1). He could escape diabetic ketoacidosis with an intravenous insulin infusion of over 1,000 U per day of human regular insulin. This high dose of intravenous insulin was required for about 2 months to prevent ketoacidosis. To evaluate the cause of severe insulin resistance, the following experiments were performed.

The aliquots of plasma were treated with polyethylenglycol (PEG) to precipitate anti-insulin antibody and allow measurement of circulating free insulin levels. Total plasma insulin was measured after acid treatment and PEG precipitation of antibodies. Total and free insulin levels in several samples were 690–1,000 and under 5 μU/ml, respectively. Percent ¹²⁵I-insulin binding to patient plasma was higher than that of the control plasma (76–80% vs <10%). Using Chinese hamster ovary (CHO) cells expressed human insulin receptors on their cell surface, anti-insulin receptor autoantibodies could not be detected in the patient plasma. Counterregulatory hormone levels including GH, cortisol, glucagon, catecholamines, and thyroid hormones were all normal. Plasma IgE level and RAST to human insulin were also normal. Skin test to human regular and NPH insulin, and drug-induced lymphocyte stimulation test (DLST) against human insulin were all negative. These results suggest that the present severe insulin resistance may be due to insulin antibody-mediated.

To further evaluate this possibility, the binding activity of circulating anti-insulin antibody was assessed by incubation of plasma with ¹²⁵I-insulin and various concentrations of unlabeled insulin and followed by precipitation with PEG. Scatchard analysis showed a curvilinearity and the maximum binding capacity was determined to be 2,900 U insulin/l (1.7×10⁻⁵ mol/l) (Fig. 2). In addition, patient plasma was tested for ability to inhibit the binding of ¹²⁵I-insulin to insulin receptors in CHO cells. Binding of insulin to receptors was reduced by 50% in the presence of only 4 μl of patient plasma, whereas over 150 μl of control plasma from a non-insulin resistant diabetic subject with insulin antibodies (Fig. 3). Since insulin receptor antibodies were absent in the present patient’s plasma, it is likely that the inhibition of ¹²⁵I-insulin binding to receptors was due to the formation of insulin and its antibody complex. These lines of evidence clearly indicated that circulating high-capacity insulin antibodies in the patient plasma induced severe insulin resistance.

On the other hand, hypereosinophilia continued during the clinical course (Fig. 1). White blood cell count was continu-
Fig. 2. Scatchard analysis of anti-insulin antibodies in the plasma before (●) and after (○) glucocorticoid therapy. K (1/U insulin) and A (U insulin/l) indicate the equilibrium constant and the antibody binding capacity, respectively.

Fig. 3. Effect of plasma from the patient before (●) and after (×) glucocorticoid therapy and from non-insulin resistant diabetic subject with insulin antibody (○) on binding of 125I-insulin to insulin receptors. 125I-insulin was incubated with CHO cells in the presence of increasing amounts of plasma. Anti-insulin antibodies in the patient plasma have a greater inhibitory effect on 125I-insulin binding to its receptors in CHO cells than those in the control subject.

ynchronously over 10,000/mm³ with 60–65% eosinophils noted. A bone marrow smear showed a hypercellular marrow with 64% eosinophils but no atypical cells. Cervical lymphnode and liver biopsy specimens revealed the infiltration of granulocytes, and many were mature degranulated eosinophils (Fig. 4A). Neither the Philadelphia chromosome nor any other chromosome abnormalities could be demonstrated. There also was no evidence that the patient was infected by parasites as determined by Ouchterony immunodiffusion using several parasite antigens. As shown in Fig. 1, at the end of May, marked hyperglycemia with ketoacidosis appeared again with the elevation of the eosinophil count. We increased intravenous insulin to 2,000 U per day and started systemic glucocorticoid therapy. Six weeks later, fasting plasma glucose levels were improved (80 to 180
Insulin Resistance in HES

Fig. 4. Histologic findings of liver biopsy specimen (A) and aortic valve after operation (B). A: Eosinophilic infiltration was shown in Glisson's sheath and extended into the sinusoid (HE stain, ×200). B: Infiltrating inflammatory cells, mainly consisting of eosinophils, were prominent in the necrotic tissue of endocardial vegetation. Bacterial colony was not seen (HE stain, ×200).

mg/dl) on 160 U of human regular insulin per day. Total eosinophil count was still high but had decreased. Both maximum binding capacity of insulin antibody (Fig. 2) and inhibitory effect of its antibody on 125I-insulin binding to the receptor (Fig. 3) were reduced after glucocorticoid therapy. Lymphnodes, liver and spleen were no longer enlarged.

The patient was discharged in August 1992 in good condition and receiving 15 mg/day of predonisolone and 160 U/day of human regular insulin. However, he was readmitted in November 1992, because of acute cardiac failure and high fever. Cardiac examination revealed suspected cardiac dysfunction due to aortic and mitral regurgitation caused by infective endocarditis. Replacement of both valve was performed, and the pathological findings indicated a perforation of the aortic valve with massive infiltration of degranulated eosinophils, but a bacterial colony was not detected (Fig. 4B). He died in December 1992 due to the progression of the heart failure.

Discussion

In the present case, severe insulin resistance was suspected due to an anti-insulin antibody. Insulin treatment of patients with diabetes mellitus usually leads to production of antibodies against insulin. However in a vast majority of patients, insulin-binding antibodies have not appeared to have had a clinical significance during treatment with highly-purified animal insulin. Even if insulin resistance developed, it was usually resolved by changing to human insulin. There have been a few reports that insulin allergy and resistance have been observed after the use of human insulin (5), which was attributed to the crossreactivity of the insulin antibody against animal insulin to human insulin. There was only one case report that insulin allergy and resistance was developed in a patient whose initial form of insulin therapy was human insulin (6). It has been postulated that immunogeneity of human insulin is caused by an altered tertiary structure, although the primary amino acid sequence of human insulin is identical to that of endogenous circulating human insulin.

The present case appears to be unique in that extreme insulin resistance with a massive insulin requirement of over 1,000 U/day occurred during the use of human insulin which was started three years prior. Berson and Yalow analyzed kinetic aspects of the reaction between insulin and its antibodies using plasma from insulin resistant and nonresistant diabetic subjects (7). In nonresistant subjects, insulin-binding capacities of antiserum generally did not exceed above 10 U insulin/l plasma, whereas it ranged from 50 to over 500 U insulin/l plasma in insulin-resistant patients. Therefore, the present patient had an extremely high capacity of binding antibodies to insulin in comparison (before therapy 2,900 U/l vs after therapy 1,250 U/l). We speculate that this increased rate of production of insulin antibody may be associated with immunological disorders observed in HES.

HES is characterized by marked peripheral blood and bone marrow eosinophilias associated with varying degrees of organ dysfunction from eosinophilic infiltration. The diagnosis of HES requires a persistent elevation in the total eosinophil count (>1,500/mm³) for over 6 months, associated organ damage and no detectable underlying cause (8). In the present case, total eosinophil counts exceeded over 5,000/mm³ for 3 years. Involvement of almost all organ systems has been reported in HES, but most commonly involved are the heart, lungs, skin and the nervous system. The present case showed aortic and mitral valvular insufficiency due to the infiltration of eosinophils. Eosinophilic infiltration was also observed in the liver and lymphnodes. In addition, crural muscle atrophy and weakness were possibly caused by tibial nerve mononeuropathy which may be involved due to eosinophilic infiltration. These findings clearly indicate that the present case satisfies the specific criteria for HES as mentioned above.

The interaction between HES and severe insulin resistance due to insulin antibodies is not well understood. In HES, extremely high levels of soluble IL-2 receptors were circulated in the plasma (9), suggesting the increased level of activated T cells. Therefore, continuous T cell activation seems to be persistent in HES and results in hyper-immunoresponses to several exogenous antigens. Since some of the patients with
HES previously suffered with allergenic diseases and parasitic infection, it is likely that continuous T cell activation may be induced by the antigen-specific stimulation which could trigger the hypereosinophilia. In the present case, insulin was administered for a short term in 1975 and about 10 years later hypereosinophilia and hepatosplenomegaly were noticeable. In 1989, when continuous insulin therapy was started, itching with redness appeared at injection sites and insulin antibodies were detectable at an early stage of treatment, while eosinophil counts were further increased at the start of insulin treatment. It is conceivable, therefore, that the resumption of insulin therapy which may originally cause HES in less than 10 years seems to deteriorate in this syndrome. Finally, the present case could be important to consider regarding not only why human insulin acts as an antigen, but also the immunologic characteristics which appeared in HES.

References